

# New Cryoem Methods to Capture Endogenous Complexes in Multiple Functional States at Atomic Resolution

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The last decade has witnessed advances in high-resolution cryoEM “revolutionizing” structural biology; as such, cryoEM has become a highly sought-after means of biochemical and biomedical investigations. Results from cryoEM are beginning to significantly enhance our understanding of the cellular processes responsible for maintenance, transmission and expression of genetic information at the atomic level. At the heart of these processes lie macromolecular complexes, within and outside the cell, which can now be studied by cryoEM. Understanding how and why these complexes function relies on visualizing their three-dimensional (3D) structures at their endogenous and multiple functional states.

Towards this end, we have developed an integrative proteomics cryoEM methods to determine atomic structures of native cellular complexes, sub-particle refinement and nucleic acid modeling methods to model genomic RNA and DNA in action. Of particular note, our cryoID method (Ho et al., Nat Methods, 2020) allows determination of atomic structures of endogenous complexes in cellular milieu, capturing their multiple states, including those in their acts of carrying out their functions. Applications of cryoID has enabled atomic structure determination of previously intractable biological systems from cellular milieu and membrane.